REMARKS

This paper is a Response to the Office Action mailed March 31, 2008. Claims 111 to 134 are under consideration. Claims 131 and 132 have been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit of priority of the subject application. New claims 135 to 154 have been added. Accordingly, upon entry of this paper claims 111 to 130, and 133 to 154 are under consideration.

Regarding the Interview

Applicants wish to thank the Examiner and supervisor for discussing all grounds for rejection of record on July 24, 2008. Applicants believe that the amended claims submitted herewith are consistent with the discussion.

Regarding the Claim Amendments

The amendments to the claims are supported throughout the specification. In particular, the amendment to claim 111 to recite that the antibody binds "to an epitope" of the recited polypeptide is supported, for example, at page 2, lines 8-9, which discloses "polypeptides which react with an epitope specific for neoplastic cells," and at page 55, lines 3-8, which discloses antigens recognized by the antibodies, more particularly, that "PM-2 reacted with proteins of about 55 kDa and 115 kDa." The amendment to claim 111 to recite that the "PM-2 antibody produced by a cell line deposited as DSM ACC2600 specifically binds to said epitope of the polypeptide having an approximate molecular weight of 115 kDa...." is supported, for example, at page 21, lines 23-26, which discloses that "....PM-2....monoclonal antibodies, and other antibodies or fragments thereof, that are specific for the antigen recognized by these antibodies...."; and at page 55, lines 3-8, which discloses antigens recognized by the antibodies, particularly that "PM-2 reacted with proteins of about 55 kDa and 115 kDa." The amendment to claim 111 to delete reference to the percent identical language was made in view of the amendments to claims 112 to 118, which recite a degree of percent identity greater than 90%, and is supported, for example, at page 16, lines 16-22. Thus, as the claim amendments are supported by the specification, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

New claims 135 to 154 essentially parallel the language of amended claims submitted herewith, except that the recited polypeptide has an approximate molecular weight of "55 kDa." Claims 135 to 154 are therefore supported throughout the originally filed specification

and claims, and as set forth above and in the record for the various claim amendments. Thus, as claims 135 to 154 are supported by the specification, no new matter has been added and entry thereof is respectfully requested.

Regarding the Priority Application

Applicants respectfully do not concede the issue of priority for the claims. In particular, for example, support for claims that refer to variant sequences, including modifications and substitutions can be found throughout DE 102 30 516.1, filed July 4, 2002. For example, claim 1 recites that the antibody comprising heavy and light chain molecules, in which "at least one variable region of the light chains has substantially the amino acid sequence stated in Appendix 2 and/or at least one variable region of the heavy chains has substantially the amino acid sequence stated in Appendix 1." Claim 8 is directed to antibodies and functional fragments according to claims 1 to 7 "characterized in that individual amino acid groups are substituted, and/or inserted, and/or removed." Furthermore, DE 102 30 516.1 discloses that "the present invention encompasses minor modifications or substitutions of the chains" at page 3, paragraph [0010] Moreover, DE 102 30 516.1 discloses that "the characteristics of the antibody or the functional fragments thereof may be modified by substituting and/or inserting and/or removing individual amino acid groups" at page 4, paragraph [0022] Thus, it is clear that the present scope of the claims are adequately supported by DE 102 30 516.1, filed July 4, 2002.

I. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claims 111 to 122 and 124 to 130 under 35 U.S.C. §112, second paragraph, as allegedly indefinite is traversed. Allegedly, the claims are indefinite because of the recitation of 55 or 110 kDa molecular weight forms.

As discussed in the record, the skilled artisan would know of a variety of plausible reasons why molecular weight of intact protein could be 110 kDa or 55 kDa. To reiterate, the antigen degraded during preparation or size fractionation by electrophoresis, forms a 55 kDa fragment. Thus, the antibody could bind to both 55 and 110 kDa molecular weight forms if the epitope is present on the intact 110 kDa protein and the 55 kDa degradation product. Another possible explanation is that the 110 kDa form represents an unprocessed protein containing the epitope, whereas the 55 kDa form represents a proteolytically processed (cleaved) version of the 110 kDa protein; again the antibody can bind to 55 and 110 kDa molecular weight forms since the epitope is present on both forms. There are other possible

explanations, all of which would be known to the skilled artisan. In view of the fact that the skilled artisan would know of several plausible explanations why the antibody binds to different molecular weight proteins, the claims would not be unclear or indefinite due to the recitation of multiple molecular weights. Consequently, claims 111 to 122 and 124 to 130 are clear and definite under 35 U.S.C. §112, second paragraph.

Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, claim 111 has been amended to only recite a 115 kDa polypeptide, and new claim 135 only recites a 55 kDa polypeptide. In view of the amendment, claims 111 to 122 and 124 to 130 are clear and definite under 35 U.S.C. §112, second paragraph, and Applicants respectfully request that the rejection be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 111 to 122 and 124 to 130 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 5-16.

The proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988)

Here, in view of the guidance in the specification and knowledge and skill in the art concerning antibody structure and function at the time of the invention, and that antibody variants having the requisite activity could be produced and identified using routine methods disclosed in the specification or that were known in the art at the time of the invention, one skilled in the art could make antibodies and antigen binding fragments that specifically bind to the recited polypeptide without undue experimentation.

First, the Examiner has acknowledged that the level of knowledge and skill with respect to antibody structure and function at the time of the invention was high. For example, as discussed at length in the Office Action the role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding were well understood by the skilled artisan at the time of the invention. The specification also discloses the role of antibody heavy and light chain variable regions, CDR and FR regions in antigen binding (page 22, line

6, to page 23, line 2). Consequently, in view of the high level of knowledge and skill in the art with respect to antibody structure and function at the time of the invention clearly the skilled artisan would be apprised of antibody regions that participate in antigen binding.

Second, in addition to the high level of knowledge and skill in the art concerning antibody structure and function, as acknowledged by the Examiner the specification discloses the locations of the CDRs in SEQ ID NOs:5 and 7 (page 7 of the Office Action). In particular, the specification discloses the CDRs in SEQ ID NOs:5 and 7 in Figures 14 and 15 (see, also, pages 5, lines 6-7 and 24-25). Furthermore, in view of the fact that the specification discloses the location of the CDRs in SEQ ID NOs:5 and 7 and that SEQ ID NOs:5 and 7 are human sequences, the skilled artisan would know the location of the FRs in SEQ ID NOs:5 and 7. Consequently, the skilled artisan would know the location of CDRs and FRs of SEQ ID NOs:5 and 7.

Third, because the knowledge and skill in the art at the time of the invention was high in terms of antibody structure and function and the location of sequences in SEQ ID NOs:5 and 7 that contribute to antigen binding would be known, the skilled artisan would also know residues in SEQ ID NOs:5 and 7 amenable to substitution and therefore, be able to predict with reasonable certainty variants of SEQ ID NOs:5 and 7 that would have at least partial binding activity. For example, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, for example, outside of or within a CDR or FR region of in SEQ ID NOs:5 and 7 would likely not destroy antigen binding activity. In addition, the skilled artisan knows that antibody FRs and CDRs can tolerate substitutions.

To corroborate that substitutions within CDRs are tolerated, submitted herewith as Exhibit A is a publication by Kipriyanov et al. (Protein Engineering 10:445 (1997)). In Exhibit A the authors report that a substitution of a cysteine residue by a serine within CDR3 of an antibody heavy chain variable region did not have an adverse effect on affinity. Thus, Exhibit A corroborates that CDRs tolerate amino acid substitutions.

To corroborate that substitutions within FRs are tolerated, submitted herewith as Exhibit B is a publication by Holmes *et al.* (J. Immunol. 167:296 (2001)). The authors of Exhibit B report several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity. Thus, Exhibit B corroborates that FRs tolerate substitutions.

To corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated submitted herewith as Exhibit C is a

publication by Wilson *et al.* (J. Exp. Med. 187:59 (1998)). The authors of Exhibit C report a number of insertions and deletions of variable heavy chains that occur naturally during affinity maturation which are tolerated. Thus, Exhibit C corroborates that heavy and light chain variable regions tolerate insertions and deletions.

To further corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated submitted herewith as Exhibit D is a publication by Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002)). The authors of Exhibit D report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated. Thus, Exhibit D corroborates that heavy or light chain variable region sequences tolerate insertions and deletions, even within a CDRs.

Consequently, in view of the guidance in the specification and the high level of knowledge and skill in the art regarding antibody structure and function, the skilled artisan would know of general regions and particular residues that would be more or less amenable to substitution and could therefore predict SEQ ID NOs:5 and 7 variants likely to have at least partial antigen binding activity without actually having to produce such variants and fragments. Given the large number of amino residues in variable regions, clearly many variants of SEQ ID NOs:5 and 7 could be readily produced without undue experimentation that have at least partial antigen binding activity.

Fourth, the level of knowledge and skill in the art regarding making antibodies and antigen binding fragments thereof was also high. For example, methods of producing antibodies and variants without undue experimentation are disclosed in the specification (page 24, line 5, to page 28, line 24). Methods of producing antibody fragments (*e.g.*, Fv, Fab, Fab' and $F(ab')_2$) were known in the art and were routine at the time of the invention. Methods of identifying antibody variants and fragments that bind antigen without undue experimentation were also known in the art and are taught by the specification. In particular, routine methods for measuring antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 45, line 24 to page 47, line 10; page 47, line 27, to page 49, line 14; page 56, lines 1-27; and page 57, line 19, to page 58, line 11). Thus, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention, one skilled in the art could readily make antibodies and antigen binding fragments that specifically bind to a polypeptide

having the recited molecular weight and expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells without undue experimentation.

Fifth, analogous to *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation, undue experimentation would not be required to produce antibody variants and fragments that bind to the recited cell types, given that 1) producing antibody variants and fragments was routine; and 2) cell binding, antibody competition and proliferation assays were routine in the art at the time of the invention. Consequently, contrary to the assertion in the Office Action where it is suggested that one skilled in the art would have to "predict in advance" the sequence of antibodies within the claims, there is no need for the skilled artisan to "predict" variants or fragments that bind to the recited antigen in order to make variants and antigen binding fragments because making antibodies and antigen binding fragments was routine and well established at the time of the invention.

Finally, Applicants wish to address the citation to *Rochester v. Searle* 358 F.3d 916 Fed. Cir. 2004, at page 8 of the Action. The facts of *Rochester* are clearly distinguishable from the claims of the subject application for many reasons. In particular, in *Rochester* the patent at issue claimed methods of using Cox-2 inhibitors for pain and inflammation control. However, in the *Rochester* patent at issue there was not a single example of a Cox-2 inhibitor disclosed. Furthermore, in the *Rochester* patent at issue there was no guidance concerning the structure of a Cox-2 inhibitor inhibitor. In stark contrast to the facts in *Rochester*, the specification discloses a structure, that of an antibody, which structure was well known to the skilled artisan at the time of the invention. Furthermore, the specification discloses a working example of an antibody. Moreover, the specification discloses the location of amino acid sequences of antibody light and heavy chain variable regions that contribute to antigen binding and maintaining antibody structure. Consequently, the facts of the subject application are clearly distinguishable from *Rochester.*

In view of the foregoing, the skilled artisan could make antibody variants and antigen binding fragments as claimed without undue experimentation. Consequently, the claims are adequately enabled under 35 U.S.C. §112, first paragraph, and Applicants respectfully request that the rejection be withdrawn.

The rejection of claims 111 to 122 and 124 to 133 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 10-16.

Claims 111 to 122 and 124 to 133 as originally filed are adequately described. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, claims 131 and 132 have been cancelled herein without prejudice, and the claims have been amended as set forth above. The rejection will therefore be addressed with respect to the amended and new claims.

The written description requirement under 35 U.S.C. §112, first paragraph is "to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, F.2d 588, 592 (CCPA 1977). A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The description needed to satisfy the requirements of 35 U.S.C. §112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.....Since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of the knowledge in the field and differences in the predictability of the science....the law must take cognizance of the scientific facts." *Capon v. Eshhar*, 418 F.3d , 1349, 1357 (Fed. Cir. 2005). Thus, an adequate written description is a factual inquiry measured by one of ordinary skill in the art, that varies with the nature and scope of the invention, taking into consideration the scientific and technologic knowledge in existence in the relevant field.

Furthermore, to satisfy the written description requirement, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988). In this regard, "(1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an

adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Thus, in view of the standard set by the court, an actual reduction to practice or disclosure of specific examples of antibodies or functional fragments within the scope of the claims is clearly not required to satisfy 35 U.S.C. §112, first paragraph.

Particularly relevant to the issue of a single species of polypeptide providing an adequate written description for a genus of polypeptides, is *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005). In *Invitrogen* the court held that a single embodiment of a protein (a reverse transcriptase (RT)) provided an adequate written description of claims directed to a genus of such proteins. The court reasoned that the single disclosed protein embodiment was adequate to satisfy the written description requirement of 35 U.S.C. §112, first paragraph because the protein had 1) sufficient correlation between structure and function; and 2) shared significant homology with others. In affirming that the patents in-issue satisfied the written description requirement, as articulated by the court in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (1997) and *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the court held that "the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features—DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient. In short, there is no error in the district court's ruling that the claims in the patents-in-suit satisfy the written description requirement of §112." Thus, even though there was only a single disclosed embodiment the claims of the patents in-issue in *Invitrogen*, which were not limited by reciting a particular amount of homology or identity to a reference sequence in the claims, were held to satisfy the written description requirement. Accordingly, in view of *Invitrogen* a single embodiment provides a written description for a genus of proteins where there is sufficient correlation between protein structure and function, and the members of the species share significant homology.

Here, the skilled artisan has substantial understanding of antibody structure and function, and the claimed antibodies and functional fragments defined by percent identity to a heavy or light chain variable region share significant sequence homology (at least 90%) with heavy or light chain variable region sequences SEQ ID NOs:5 and 7. Furthermore, the specification discloses a working example having binding activity within the genus.

Consequently, given the correlation between antibody structure and function, that the antibodies defined by percent identity share significant sequence homology to SEQ ID NOs:5 or 7, and that the specification discloses an embodiment within the genus having binding activity, clearly the claims meet the written description standard as articulated by the court in *Invitrogen*. Consequently, claims 111 to 130 and 133 are adequately described.

As discussed above, the specification teaches antibody heavy and light chain variable sequences (e.g., SEQ ID NOs:5 and 7). The specification also teaches the position of the three CDRs in each heavy and light chain variable region sequence, and therefore the position of the flanking regions (FR). In view of the foregoing guidance, one skilled in the art would know the location of the amino acid sequences that contribute to antigen binding.

As also discussed above, the level of knowledge and skill in the art with respect to antibody structure and function was high at the time of the invention. Evidence of such knowledge, such as native antibodies having two heavy and light chain sequence, the presence and contribution of three CDRs to binding, and the role of FRs is acknowledged in the Office Action and is taught by the specification. Thus, in view of the high degree of knowledge and skill in the art concerning antibody structure and function at the time of the invention, when combined with the guidance of the specification of the heavy and light chain variable sequences, SEQ ID NOs:5 and 7, the location of the CDRs and FRs that contribute to antigen binding, the molecular weights of the antigen and the cells types expressing the antigen, and the high degree of sequence identity to SEQ ID NOs:5 or 7, the skilled artisan would know variants of SEQ ID NOs:5 and 7 that would retain least partial antigen binding activity, as discussed above and in the record. Consequently, the skilled artisan would be apprised of a number of antibodies and antigen binding fragments within the scope of the claims.

In terms of a description of the claimed antibodies and antigen binding fragments to distinguish them from other materials, the antibodies and antigen binding fragments are described 1) structurally- they have heavy and light chain variable region sequences, and may have at least 90% identity to SEQ ID NOs:5 or 7; and 2) functionally- they bind to a polypeptide having an approximate molecular weight of 55 or 110 kDa using SDS-PAGE, and the polypeptide is expressed by ASPC-1 or BXPC-3 cells. Thus, as the claimed antibodies and antigen binding fragments are described structurally and functionally, the antibodies and antigen binding fragments are adequately distinguished from other materials.

In terms of the concern regarding a description of the antigen to which the antibodies bind, as discussed above the polypeptide is defined in terms of molecular weight. As also discussed above, the polypeptide is expressed by the specified cell types. Finally, the polypeptide is defined based upon its binding to antibody comprising SEQ ID NOs:5 and 7. Thus, the antigen is described in terms of the specified molecular weight, cell type expression and the antibody that the antigen binds.

Furthermore, as discussed above the written description requirement may be satisfied without examples or an actual reduction to practice. Consequently, clearly the written description requirement of 35 U.S.C. §112, first paragraph can be satisfied without actually isolating or sequencing the antigen to which the claimed antibodies and fragments bind.

In sum, in view of the guidance in the specification and the substantial understanding of antibody structure and function at the time of the invention, and the degree of sequence identity of the claimed antibodies and functional fragments to SEQ ID NOs:5 or 7, as corroborated by Exhibits A-D, the skilled artisan would be apprised of a number of antibodies and functional fragments of claims . Furthermore, in view of the substantial understanding of antibody structure and function, the significant sequence homology required by the dependent claims, and that the specification discloses an embodiment having activity, clearly the claims meet the standard for written description articulated by the court in *Invitrogen*. Consequently, claims 111 to 122, 124 to 130 and 133 are adequately described under 35 U.S.C. §112, first paragraph, and Applicants respectfully request that the rejection be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. §102

The rejection of claims 111 to 122 and 126 to 132 under 35 U.S.C. §102(a) as allegedly anticipated by Brandlein *et al.* (Human Antibodies 11:107 (2002)) is respectfully traversed. The rejection of claims 123, 133 and 134 under 35 U.S.C. §102(a) as allegedly anticipated by Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) as evidenced by Brandlein *et al.* (Human Antibodies 11:107 (2002). Allegedly, Brandlein *et al.* describe each and every element claimed, as set forth on pages 16-17 and 21-22 of the Office Action.

Claims 111 to 123 and 126 to 134 are adequately supported by the priority application, as discussed above and in the record. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection,

claims 131 and 132 have been cancelled herein without prejudice, and the claims have been amended as set forth above. The rejection will therefore be addressed with respect to the amended and new claims.

Brandlein *et al.* (Human Antibodies 11:107 (2002)) was not published prior to July 4 or 6, 2002, the filing dates of the German priority applications. Rather, according to an email from Ms. Susan Hendriks, marketing Coordinator at IOS Press, the publisher of the journal Human Antibodies, "Volume 11, number 4 of Human An[ti]bodies was published on April 18th 2003." Furthermore, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) was also not published more than one year prior to the July 4 or 6, 2002 filing dates of the German priority applications.

Submitted herewith is a Declaration under 35 C.F.R. §1.132, executed by Drs Vollmers and Mueller-Hermelink which declares, among other things, that to the extent, if any, that Brandlein *et al.* (Human Antibodies 11:107 (2002)) and Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) describe or suggest the subject matter claimed in the above-identified U.S. patent application, the subject matter described or suggested in the Brandlein *et al.* references was derived from us, and was invented by us, rather than the other authors of the Brandlein *et al.* references. In view of the executed Declaration under 35 C.F.R. §1.132, Brandlein *et al.* (Human Antibodies 11:107 (2002)) is not prior art against claims 111 to 122 and 126 to 130, and Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) is not prior art against claims 123, 133 and 134 under 35 U.S.C. §102(a). Consequently, Applicants respectfully request that the rejections under 35 U.S.C. §102(a) be withdrawn.

The rejection of claims 111 to 122 and 126 to 132 under 35 U.S.C. §102(b) as allegedly anticipated by Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) as evidenced by Brandlein *et al.* (Human Antibodies 11:107 (2002)) is respectfully traversed. Allegedly, Brandlein *et al.* describe each and every element claimed, as set forth on pages 17-19 of the Office Action.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990), *In re Bond*, 910 F.2d 831 (Fed. Cir. 1990). Furthermore, a reference cited under section 102 must contain an enabling disclosure. *citations omitted*, see, M.P.E.P. §2121.

Claims 111 to 122 and 126 to 132 are adequately supported by the priority application, as discussed above and in the record. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, claims 131 and 132 have been cancelled herein without prejudice, and the claims have been amended as set forth above. The rejection will therefore be addressed with respect to the amended and new claims.

As a first issue, Applicants respectfully point out that a reference cited under 35 U.S.C. §102 must have an enabling disclosure. Thus, for this rejection to be proper, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) must enable one skilled in the art to make and use claims 111 to 123 and 126 to 130 without undue experimentation. However, these claims have also been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Consequently, the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §112, first paragraph are contradictory and cannot be maintained simultaneously. Applicants therefore respectfully request that the Patent Office withdraw either the rejection under 35 U.S.C. §102(b) or the rejection under 35 U.S.C. §112, first paragraph.

As a second issue, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) at best mention the term "PM-2"- there is no information concerning the nature of the antigen to which PM-2 binds, such as molecular weight. Nor is there any information in the abstract concerning how to produce PM-2 antibody or a source of PM-2 antibody, or a heavy or light chain variable region sequence, such that one skilled in the art could obtain or produce PM-2 antibody or a variant antibody or subsequence thereof, without undue experimentation. Absent antigen information, antibody sequence or a source or method to obtain or produce PM-2 antibody one skilled in the art could not produce the antibody without undue experimentation. Consequently, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to enable claims 111 to 123 and 126 to 130.

In sum, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to enable claims 111 to 123 and 126 to 130. As such, the rejection under 35 U.S.C. §102(b) is improper and must be withdrawn.

IV. REJECTION UNDER 35 U.S.C. §103(a)

The rejection of claims 124 and 125 under 35 U.S.C. §103(a) as allegedly obvious over Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) in view of

Taylor *et al.* (US Patent 5,001,225) is respectfully traversed. Allegedly, Brandlein *et al.* in combination with the secondary reference teach or suggest each and every element claimed, as set forth on pages 19-21 of the Office Action.

In order for a rejection to be proper under 35 U.S.C. §103(a), there must have been at the time of the invention: 1) a suggestion or motivation to modify or combine the references at the time of the invention; 2) a reasonable expectation of success of producing the claimed invention; and 3) the combined references must teach or suggest each and every claim limitation. Both the teaching or suggestion to make the claimed combination and reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. See, e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988). [R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006); *see also, KSR International Co., v. Teleflex Inc.*, 82 U.S.P.Q. 1385, 1396 (U.S. 2007)- "a patent composed of several elements is not proved obvious by merely demonstrating that each of its elements was, independently, known in the prior art.

Here, among other things, there would not have been a reasonable expectation of success of producing the claimed antibodies in view of Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)). As discussed above, the cited abstract fails to teach or suggests anything concerning the nature of the antigen to which PM-2 binds. Nor is there any information in the cited abstract concerning how to produce PM-2 antibody or a source of PM-2 antibody. Furthermore, the abstract fails to describe any heavy or light chain variable region antibody sequences. Thus, in view of the foregoing deficiencies, one skilled in the art could not obtain or produce PM-2 antibody or a variant antibody or subsequence thereof with a reaosnable expectation of success. Consequently, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to teach or suggest each and every element of claims 124 and 125.

The secondary reference of Taylor *et al.* (US Patent 5,001,225) fails to provide that which is missing from Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)). In this regard, there is no sequence described in Taylor *et al.* at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7. Consequently, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) and Taylor *et al.* (US Patent 5,001,225) fail to teach or suggest each and every element of claims 124 and 125.

Lastly, if the Patent Office maintains that one skilled in the art would have been able to obtain PM-2 antibody based upon the cited abstract and Taylor *et al.* (US Patent 5,001,225) at the time of the invention, Applicants respectfully again note that "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) Thus, the Office must explain how the antibody would have been obtained or produced, given the information in the cited abstract and Taylor *et al.* (US Patent 5,001,225), at the time of the invention.

In sum, Brandlein *et al.* (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) alone or in combination with Taylor *et al.* (US Patent 5,001,225) fail to teach or suggest each and every element of claims 124 and 125, and fail to provide a reasonable expectation of success of producing an antibody or an antigen binding fragment of claims 124 and 125. As such, the rejection under 35 U.S.C. §103(a) is improper and Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065. Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP

ROBERT M. BEDGOOD
Reg. No. 43488
Tel. No. 858.509.4065
Fax No. 858 509.4010

Date: September 30, 2008
12255 El Camino Real
Suite 300
San Diego, CA 92130
(619) 234-5000